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	First Named Inventor	WOLBER, PAUL K.
	Examiner	CROW, ROBERT
	Group Art	1634
	Title: NUCLEIC ACID ARRAYS COMPRISING DEPURINATION PROBE FEATURES AND METHODS FOR USING THE SAME	

Sir:

This Supplemental Reply Brief is in response to the Examiner's Answer sent by the Office on February 27, 2008.

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REPLY BRIEF

In this Reply Brief, the Appellants address several issues raised in the second Examiner's Answer. The Appellants note that all arguments presented in the prior Appeal Brief still apply with equal force, but are not reiterated here solely in the interest of brevity and for the convenience of the Board.

In their Appeal Brief, the Appellants argued that in attempting to establish this rejection, the Examiner proposed to modify McGall's method in a way that would either change the principle of operation of McGall's method, or render McGall's method inoperative. Briefly, the Examiner proposes to modify McGall's method from one in which depurination is measured by the release of a terminal label from an immobilized labeled nucleic acid, to another in which depurination is measured by cleavage of a complex containing an unlabeled immobilized nucleic acid and a hybridized labeled probe. While both methods (i.e., McGall's method and the claimed method) may rely on cleavage, the proposed changes to McGall's method would either change the principle of operation of McGall's method, or render McGall's method inoperative. For example, the Examiner proposed to replace McGall's terminally labeled, immobilized nucleic acid with an unlabeled nucleic acid. That modification, in itself, would render McGall's method inoperable because there would be label and therefore no way for McGall to detect depurination. In the Examiner presents no reason why this argument lacks force and, as such, it is believed that this argument stands firm. Reversal of this rejection is therefore requested. Further arguments for patentability have been presented and are discussed below.

In the second Examiner's Answer, arguments are made in sections denoted A through H. The Examiner's assertions are therefore addressed herein in the same format. Each section represents a separate and independent reason why the remaining rejections should be withdrawn.

A. In response to Appellants' statement that McGall, in the full knowledge of nucleic acid hybridization, nevertheless explicitly teaches that the way to measure

depurination is the direct chemical labeling of in situ oligonucleotides and quantitation of how much label remains after exposure to a depurinating condition, the Examiner simply reiterates arguments made in the first Examiner's Answer filed October 11, 2007. In the cited passage (page 8-9), the Examiner attempts to establish that "a test condition" can be "an operating condition" according to McGall, so that the Examiner can then further establish that "hybridization" is also an "operating condition" according to McGall, and therefore can be a "test condition."

However, Appellants point out that whether the Examiner succeeds in establishing this connection or not is irrelevant, because the Examiner's interpretation of "test condition" is flawed. Specifically, the Examiner's interpretation of "test condition" does not consistently correspond to the definition of the term used by McGall itself in the context of depurination, as discussed in the previous Reply Brief and further reviewed below.

Appellants first point out that the nature of the cited "test conditions," as it relates to depurination, to which the oligonucleotides of McGall can be exposed either after labeling and before exposure to depurination conditions (McGall, column 2, line 58) or during *in situ* synthesis (McGall, column 3, line 1) is clearly defined by McGall, and does not include hybridization. The final paragraph of the section entitled "Rates of Depurination" is reproduced below for convenience:

> Various conditions used in the synthesis of a chip can be tested for the extent to which they cause depurination. For example, one method of making chips involves coating an area with a material that generates an acid upon exposure to light. Acids cause removal of acid-labile protective groups, but they also should be chosen not to cause depurination. Therefore, particular acids used in the production of chips can be tested by this method for the extent to which they cause depurination. For example, photo-acid generating ("PAG") polymer films having a photo-activatable acid, such as those used as photo-resists in the semi-conductor industry, can be applied to various areas of the substrate in order to test the effect of particular acids in the deprotection process.

As such, it is clear that the test conditions which McGall discusses with respect to depurination have no relation to hybridization of probes or nucleotides, but

rather to pH and materials. McGall teaches that depurination which *results from exposure to these test conditions* is assessed by detection of remaining signal from the chemically modified surface-bound oligonucleotides.

The Examiner's hypothetical "single exemplary embodiment" which is allegedly assembled as a result of the combined teachings of McGall and Weng illustrates how the Examiner's logic is misguided:

The Examiner states that "the two ensembles of oligonucleotides in two areas of an array of McGall are both subjected to the *same* hybridization test condition of Weng et al." (emphasis here added). Yet in the very next sentence, the Examiner then states that "the ensemble in the first area is subjected to cleavage of depurination products." The condition which causes the "cleavage of depurination products" *is* the "test condition" according to McGall. As such, the Examiner's description of the alleged single exemplary embodiment does not maintain consistency with the teachings of the references. Specifically, the Examiner first states that "two areas of an array of McGall are both subjected to the *same* hybridization test condition of Weng et al." The Examiner then posits that "the ensemble in the first area is subjected to cleavage of depurination products;" but if this is the case, then the test conditions are *not* the same, because one area is exposed to cleavage conditions while the other is not. Put simply, the Examiner first states that test conditions are the same, and in the next sentence states that they are not. The Examiner has employed two mutually incompatible meanings of "test condition," only one of which is validated by the teachings of McGall.

Accordingly, by conflating "hybridization" (the asserted means of measuring depurination) with "test condition" (the experimental condition which causes the depurination according to McGall) into a single concept in an attempt to arrive at the instant claims, the Examiner has changed the operating principle of the primary reference, specifically, from that of measuring depurination under a test condition which causes depurination to measuring depurination *by means of* a "test condition" (assertedly, hybridization). This internal inconsistency is clear evidence that the

Examiner has changed the operating principle of the reference. Specifically, the method of McGall cannot work if the test condition – which varies from assay to assay so that it can be tested (McGall, column 10, lines 21-22) – is *also a means to measuring depurination*, i.e. the asserted hybridization of Weng.

As such, the Examiner's argument constitutes quintessential cherry-picking. Instead of considering the reference as a whole, the Examiner has abstracted a single concept – "test condition" – from McGall and generated novel and demonstrably unintended meanings for it in order to arrive at Appellants' invention. In contrast, the references, when considered as a whole as the law requires, teach that a test condition for depurination is a condition that may cause depurination (McGall). Neither McGall nor Weng teach that hybridization causes depurination.

Moreover, the Examiner reiterates in the present communication that:

> "while McGall testing the array to detect depurination (i.e., as a test condition; column 9, lines 22-65), that more than one test condition is applied (column 11, lines 20-41), that test conditions include operating conditions (column 11, lines 20-41), and wherein operating conditions of the array includes hybridization of nucleic acids to the array (column 13, lines 33-57), McGall does not explicitly show hybridization as a test condition for determining depurination" (second Examiner's Reply, page 1).

As such, the Examiner has asserted that: a) McGall teaches that test conditions include operating conditions; b) McGall teaches that operating conditions includes hybridization of nucleic acids to an array. As such, according to the Examiner's logic, McGall itself teaches that hybridization can be a "test condition."

In establishing this, the Examiner cites a section of McGall (column 13, lines 33-57) which discusses hybridization of a labeled target oligonucleotide with an oligonucleotide in an array. The Examiner then acknowledges that McGall does not

explicitly show hybridization as a test condition for determining depurination, for which element the Examiner turns to Weng.

Yet the teachings of Weng are no different in any relevant way from what has just been cited in McGall: Weng simply teaches hybridization of a labeled target oligonucleotide with an oligonucleotide in an array.

Assuming, *arguendo*, that Weng does teach hybridization as a "test condition," Weng not only fails to explicitly teach hybridization as a test condition for determining depurination, the element for which the Examiner allegedly turned to Weng, Weng is *entirely silent* regarding depurination. The reference is entirely unrelated to depurination. The Examiner seems to imply that it is relevant that Weng teaches hybridization as a means to "quality control," yet a mere description of "quality control" of array manufacture using "test conditions" in either reference is not sufficient to teach or suggest the instant claims to the ordinarily skilled artisan in light of the teachings of McGall. There are many parameters along which the quality of array manufacture might vary, and at least as many conditions under which to test such parameters. As discussed, McGall explicitly teaches that the measurement of depurination is accomplished by chemically labeling *in situ* synthesized oligonucleotides prior to cleavage. As acknowledged by the Examiner, McGall at no point teaches or suggests hybridization with a probe as a means of testing depurination, *even while recognizing that quality control of arrays can involve testing hybridization* (McGall, column 1, lines 49-51 and column 13, lines 34-51, as cited numerous times by the Examiner). One of ordinary skill in the art would find no reason in Weng to modify the teachings of McGall in any way. The disclosure of Weng identifies no problem or issue in the disclosure of McGall which McGall does not *already address by using a method which is conceptually distinct from that of the instant claims*.

Simply put, Weng remedies no conceptual gap that is not already filled by McGall itself according to the Examiner; yet by the Examiner's own admission, McGall fails to teach the limitations of the claims.

Appellants concur, and note that the reason for this failure to teach is that no discussion of “test conditions” out of context can make McGall teach that hybridization is a test condition for depurination, when McGall unambiguously teaches to the contrary. The inventive insight that depurination can be detected by forming binding complexes of the depurination probe and a target nucleic acid in a depurination probe feature to determine the presence of depurination reaction products on the surface, as claimed, is simply absent from both references and their combination.

Thus, the Appellants’ prior arguments still stand with equal force. The Appellants submit that all remaining rejections may be withdrawn on this basis alone.

B. Appellants indicated on page 7 of the Reply Brief, and reiterated above, that the citation from McGall (column 10, lines 20-35) regarding "Rates of Depurination" has no relation to hybridization of probes or nucleotides.

In response, the Examiner states that the citation describes "[v]arious conditions used in the synthesis of a chip can be tested for the extend to which they cause depurination. For example..." The Examiner states that the phrase "for example" indicates that the list of depurination conditions is not limiting and describes only several possible non-limiting embodiments that do not exclude hybridization as a test condition.

Appellants respond that failure to exclude an element does not constitute teaching of that element. As discussed in detail above, in light of the fact that McGall elsewhere in the same reference teaches measurement of depurination, it is significant that hybridization is not included in the cited passage, and, moreover is dissimilar in kind from the conditions of which are included, namely acid conditions of chip synthesis and deprotection which *can cause depurination*. Neither McGall nor

Weng teach that "hybridization" causes depurination, nor is such considered reasonable by the ordinarily skilled artisan.

C. In response to Appellants' statement that column 4, lines 58-67 of Weng does not in fact teach using hybridization as a test condition, but instead teaches *correcting for hybridization artifacts* by using other methods, i.e. fluor reversal, comparison of the same hybridization using different fluors, where these variations are the "test conditions" of Weng, the Examiner states that Weng is merely relied upon for use of the array in a hybridization assay which is an example of operating conditions. Appellants have addressed this assertion in full in section A, above. Briefly, even assuming, *arguendo*, that Weng does teach hybridization as a "test condition," Weng not only fails to explicitly teach hybridization as a test condition for determining depurination, the element for which the Examiner allegedly turned to Weng, Weng is *entirely silent* regarding depurination. Accordingly, whether Weng teaches hybridization as a "test condition" is immaterial in light of the fundamental deficiencies of Examiner's argument as detailed above.

D. In response to Appellants' argument that the Examiner has changed the operating principle of the primary reference, the Examiner asserts that the arrays of McGall are clearly used for hybridization (column 13, line 34-60), and thus the operating conditions of the array include hybridization conditions, and the operating principle has not been changed by the examiner because the array is used in the manner for which it was designed; namely, hybridization.

Appellants respond that whether the arrays of McGall can be used for hybridization is not at issue; indeed, Appellants have cited passages of McGall in their own arguments which state precisely such. This does not change the fact that neither McGall nor Weng anywhere teach or suggest the use of hybridization complexes in measuring depurination, as is claimed.

E. In response to Appellants' argument that a mere description of "quality control" of array manufacture using "test conditions" in not sufficient to teach or suggest the instant claims because McGall suggests other ways to address quality control without explicitly teaching the use of hybridization and Weng is entirely silent regarding depurination, the Examiner simply reiterates the previously made argument regarding how a "test condition" can be "an operating condition" according to McGall, so that "hybridization" is also an "operating condition" and therefore a "test condition." The deficiencies of this argument have already been fully addressed above in section A.

F. The Examiner reiterates the assertion that Appellants agree "that the removal of depurination oligonucleotides and determination of the amount of depurination are test conditions according to McGall."

In seeking to support this assertion, Examiner quotes page 9 of the Appeal Brief, which states that "to the extent that McGall discloses determining the amount of depurination, it is with respect to subjecting the substrate to a test condition, *and then* determining the extent of any resultant depurination by quantitating any oligonucleotides which remain attached to the substrate" (emphasis here added).

In view of this passage, the Examiner asserts that "Appellant is, in fact, stating that test conditions include subjecting the substrate to a test condition, and then determining the extent of any resultant depurination by quantitating any oligonucleotides which remain attached to the substrate."

Appellants respond that the Examiner's continued assertion highlights the failure to distinguish between: 1) a test condition as described by McGall, which *causes depurination*; and 2) a means of determining (i.e. testing) *whether depurination has occurred*. As discussed in detail above, the former is supported by McGall as a test condition, the latter is nowhere described in either reference as a "test condition" for depurination.

Moreover, it would be clear *a priori* to the ordinarily skilled artisan that, if "*test conditions include subjecting the substrate to a test condition*" as stated by the Examiner, there is more than one definition of "test condition" at work. As discussed, only one such definition finds support in the references.

G. In response to Appellants' argument that the Examiner has changed the operating principle of the primary reference, the Examiner asserts that the arrays of McGall are clearly used for hybridization (column 13, line 34-60), and thus the operating conditions of the array include hybridization conditions, and the operating principle has not been changed by the examiner because the array is used in the manner for which it was designed; namely, hybridization.

Appellants respond that whether the arrays of McGall can be used for hybridization is not at issue; indeed, Appellants have cited passages of McGall in their own arguments which state precisely such. This does not change the fact that neither McGall nor Weng anywhere teach or suggest the use of hybridization complexes in measuring depurination, as is claimed.

H. The Examiner maintains that claims 21 and 23-25 do not "require hybridization as a test condition for depurination", merely requiring detecting the presence of binding complexes of the nucleic acid ligand and the analyte on the surface of the array to detect the presence of the nucleic acid analyte in the sample, and therefore the alleged deficiency of McGall with regard to independent claim 1 is moot with regard to independent claim 21 because the determination of depurination is not within the scope of claim 21.

The Examiner alleges that "while the array also has depurination probes, **claims 21 and 23-25 do not require anything to bind to the depurination probe, nor is the binding used to determine the presence of depurination reaction**

products (emphasis added by the examiner)." Thus, the alleged deficiency of McGall with regard to independent claim 1 is moot with regard to independent claim 21 because the determination of depurination is not within the scope of claim 21.

Appellants point out that claim 21 specifically recites "a nucleic acid ligand that specifically binds to said nucleic acid analyte with a sample suspected of comprising said analyte under conditions sufficient for binding of said analyte to said nucleic acid ligand on said array to occur," and further, "detecting the presence of binding complexes of said nucleic acid ligand and said analyte on the surface of said array." Appellants submit that the ordinarily skilled artisan is well aware that hybridization is how "binding complexes of said nucleic acid ligand and said [nucleic acid] analyte" form, and that the claimed "depurination features" and "depurination probe" function to detect depurination by hybridization, particularly in light of the specification.

Contra the Examiner, reading the claims in a manner that gives weight to the inherent functionality of the recited steps in light of the plain meaning of the terms as defined in the specification does not constitute "limitations from the specification … read into the claims" as the Examiner suggests. It is inherent that the recited steps produce detection of any depurination products, but particularly in light of the specification.

In view of the foregoing discussion, the Applicants request that all remaining rejections be reversed and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: April 11, 2008

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